Received: 28 May 2021 | Accepted: 31 December 2021

DOI: 10.1111/1365-2664.14125

Journal of Applied Ecology | BRITISH ECOLOGICAL SOCIETY

RESEARCH ARTICLE

Epidemiological differences between sexes affect management efficacy in simulated chronic wasting disease systems

Will Rogers[1] | **Ellen E. Brandell**[2,3] | **Paul C. Cross**[4]

[1]Department of Ecology, Montana State University, Bozeman, MT, USA

[2]Department of Biology, Center for Infectious Disease Dynamics, Pennsylvania State University, University Park, PA, USA

[3]Wisconsin Cooperative Wildlife Research Unit, Department of Forest and Wildlife Ecology, University of Wisconsin-Madison, Madison, WI, USA

[4]U.S. Geological Survey, Northern Rocky Mountain Science Center, Bozeman, MT, USA

Correspondence
Paul C. Cross
Email: pcross@usgs.gov

Funding information
U.S. Geological Survey

Handling Editor: Hamish McCallum

Abstract

1. Sex-based differences in physiology, behaviour and demography commonly result in differences in disease prevalence. However, sex differences in prevalence may reflect exposure rather than transmission, which could affect disease control programmes. One potential example is chronic wasting disease (CWD), which has been observed at greater prevalence among male than female deer.
2. We used an age- and sex-structured simulation model to explore harvest-based management of CWD under three different transmission scenarios that all generate higher male prevalence: (1) increased male susceptibility, (2) high male-to-male transmission or (3) high female-to-male transmission.
3. Both female and male harvests were required to limit CWD epidemics across all transmission scenarios (approximated by R_0), though invasion was more likely under high female-to-male transmission.
4. In simulations, heavily male-biased harvests controlled CWD epidemics and maintained large host populations under high male-to-male transmission and increased male susceptibility scenarios. However, male-biased harvests were ineffective under high female-to-male transmission. Instead, female-biased harvests were able to limit disease transmission under high female-to-male transmission but incurred a trade-off with smaller population sizes.
5. *Synthesis and applications*. Higher disease prevalence in a sex or age group may be due to higher exposure or susceptibility but does not necessarily indicate if that group is responsible for more disease transmission. We showed that multiple processes can result in the pattern of higher male prevalence, but that population-level management interventions must focus on the sex responsible for disease transmission, not just those that are most exposed.

KEYWORDS
chronic wasting disease, demography, disease ecology, epidemiology, harvest management, sex effects, simulation

1 | INTRODUCTION

Heterogeneity in disease susceptibility and infectiousness can play a large role in disease dynamics and the efficacy of control measures (Lloyd-Smith et al., 2005; VanderWaal & Ezenwa, 2016). Sex differences in resource use, space use or contact patterns result in varying exposure to pathogens (Guerra-Silveira & Abad-Franch, 2013) and therefore can drive transmission and infection heterogeneities. Sex can also drive physiological differences in sex hormones (e.g. testosterone and oestrogen) which can modulate immunological responses to infection (Foo et al., 2017) and disease-induced mortality rates (McDonald et al., 2014). While epidemiological characteristics are often difficult to measure, correlates with susceptibility or infectiousness (like sex) can help guide management in disease-affected systems particularly when test-and-cull strategies are not viable (Wolfe et al., 2004).

Sex is a potentially important factor in the spread of chronic wasting disease (CWD; Potapov et al., 2013), a transmissible spongiform encephalopathy that can affect all members of the *Cervidae* family (Miller et al., 2000; Williams & Young, 1980). CWD poses a serious management challenge because CWD-affected populations may be less demographically viable (DeVivo et al., 2017; Edmunds et al., 2016), hosts are asymptomatic but infectious for months (Tamgüney et al., 2009), and the infectious prion causing CWD can persist for years to decades in the environment (Miller et al., 2000; Williams, 2005). Without a vaccine or treatment, altered harvest regulations are one of only a few tools available to wildlife managers (Mysterud & Rolandsen, 2018; Uehlinger et al., 2016; Williams et al., 2002).

As evidence of the sex effect in CWD epidemiology, males are often 1.5–3 times more likely to be infected with CWD compared to females among white-tailed deer *Odocoileus virginanus*, mule deer *O. hemionus* and reindeer *Rangifer tarandus*, though the source of this variation is unknown (DeVivo et al., 2017; Heisey et al., 2010; Miller & Conner, 2005; Miller et al., 2008; Mysterud et al., 2019; Rees et al., 2012; Samuel & Storm, 2016); though, this pattern is not ubiquitous (see Edmunds et al., 2016). Sex-specific differences in immune response (e.g. hormonal immunomodulation) are an unlikely explanation of male-biased prevalence, and, although host genetics can determine CWD susceptibility and clinical progression (Robinson et al., 2012), there is no evidence that variation in this gene meaningfully differs between sexes. Consequently, it is more likely that behavioural, not physiological, differences between males and females drive greater male prevalence.

The behavioural ecology of *Cervidae* suggests evidence for many behaviourally mediated transmission scenarios. Higher male-to-male transmission may occur due to the formation of bachelor groups whereby males spend more time with other males outside of the mating season (Clutton-Brock et al., 1987) or through competition with other males for mates (de Vos et al., 1967). Members of *Cervidae* are also sexually dimorphic and males generally consume more resources and have larger home ranges than females (Relyea et al., 2000), potentially increasing environment-to-male transmission rates. While females are likely to spend more time with females than males during the year, it remains unclear which behaviours are most associated with disease transmission and whether time spent is a good proxy for exposure risk. For example, higher female-to-male transmission may be due to reproductive behaviours during the mating season whereby infectious prions are recovered from urine and facial and leg exocrine glands of white-tailed and mule deer (de Vos et al., 1967), all of which may be of particular interest to males during the mating season.

Chronic wasting disease transmission between sexes is critical for determining the intensity of sex-specific harvests (Potapov et al., 2016). At least three hypothetical processes exist which result in male-biased prevalence, including (1) males are more exposed or susceptible to infection, regardless of the source; (2) higher male-to-male transmission than male-to-female or female-caused transmission (e.g. females infecting other males or females) or (3) higher female-to-male transmission than female-to-female transmission or male-caused transmission (Potapov et al., 2013; Samuel & Storm, 2016). Harvest strategies which underestimate female contributions to CWD transmission may not be effective in reducing prevalence and will likely have delayed demographic costs associated with chronic disease in adult age classes. Conversely, if females contribute significantly to CWD transmission, managers must balance the epidemiological benefit of female harvests with associated demographic costs—an important consideration, as population viability in *Cervidae* is generally most sensitive to adult female survival (Chitwood et al., 2015; Raithel et al., 2007).

We aimed to better understand how sex-biased harvests affect CWD with different transmission scenarios between sexes, as well as examine how well prevalence measurements (i.e. what managers might perceive) capture differences in transmission and harvest scenarios. To do this, we used a sex- and age-structured mechanistic model to simulate population and CWD infection dynamics under three prion transmission scenarios with varying rates of male and female harvests. We evaluated the success of different harvest regimes based on prevalence, epidemic growth rate and host population size. Finally, we simulated sex-biased harvests under separate transmission dynamics to determine whether changes in prevalence patterns across harvest strategies can provide insights into the mechanisms of disease transmission.

2 | MATERIALS AND METHODS

We developed a discrete, demographically structured model to simulate CWD dynamics in mule deer and elk *Cervus canadensis* populations. The model operated on a monthly time step, where the order of events was reproduction, natural mortality, harvest-related mortality, disease-related mortality and disease transmission. The model began in May with births occurring only in June and harvest occurring only in November. Individuals progressed to the next age class in May.

We created a pre-breeding, two-sex Leslie matrix with 12 age categories ($c = 1, 2, 3, \ldots, 12$) for females ($s = F$) and males ($s = M$;

described in Figure S1), informed by published estimates of elk and mule deer sex- and age-based survival, fecundity and sex ratio at birth in North America (Bender & Hoenes, 2018; Bishop et al., 2005; Forrester & Wittmer, 2013; Pojar & Bowden, 2004; Raithel et al., 2007; Unsworth et al., 1999; White et al., 1987; see Table S1). Results shown in the main text describe simulations assuming mule deer demographic parameters (see Supporting Information for elk demographic simulations). Survival to the next age category was determined by survival ($\delta_{s,c}$) and the probability of harvest mortality ($\kappa_{s,c}$). Fecundity was assumed to be equal for infected and healthy individuals (Edmunds et al., 2016).

Transmission between sexes was determined by a baseline coefficient β and a dyadic sex-specific multiplier, γ_{ab}, where a is the sex of the transmitter and b is the sex of the receiver (Table S2). As shorthand, we write the transmission coefficient (e.g. $\gamma_{a=M,b=F}$) as a condensed form for presentation (e.g. γ_{MF}). Multiplier values selected all generated 1.5–2 times greater CWD prevalence in adult males than females (Figure 1). 'Equal transmission' considered male-to-male transmission to be equivalent to female-to-male transmission (γ_{MM} and $\gamma_{FM} = 2$), while male-to-female and female-to-female transmission were weighted less ($\gamma_{MF} = 1$ and $\gamma_{FF} = 1$). 'Male-dominated' transmission considered male-to-male transmission to be fourfold that of female-to-female ($\gamma_{MM} = 4$), and male-to-female transmission was weighted less than male-to-male transmission ($\gamma_{MF} = 2$), but still more heavily weighted than female-to-male or female-to-female transmission ($\gamma_{FF} = 1$ and $\gamma_{FM} = 1$). 'Female-dominated' transmission considered female-to-male ($\gamma_{FM} = 2$) transmission to be more heavily weighted than female-to-female transmission ($\gamma_{FF} = 1$), and that male-to-male and male-to-female transmission were weighted less than female-to-male transmission (γ_{MM} and $\gamma_{MF} = 0.5$). Transmission coefficients between sex categories were assumed to be constant across the year for all age classes and disease classes (Samuel & Storm, 2016).

Chronic wasting disease-infected individuals typically die 1–3 years after infection (Williams & Young, 1980; Williams et al., 2002). To model this, we used multiple infectious subcategories to create a unimodal gamma distribution of time to disease-induced mortality, rather than an exponential distribution of time until death (Wearing et al., 2005). We defined 10 disease categories, d, with new infections transitioning from susceptible, $S_{t,s,c}$, though $d = 1$ to $d = 10$. Individuals progressed through each of these categories at a monthly rate, ρ. Individuals progressed at this same rate beyond $d = 10$, constituting CWD-induced mortality. At the outset of a simulation, all infected individuals started in $d = 1$. We assumed disease-induced mortality did not depend on age or sex. The value of ρ used in our simulations ($\rho = 0.43$) resulted in

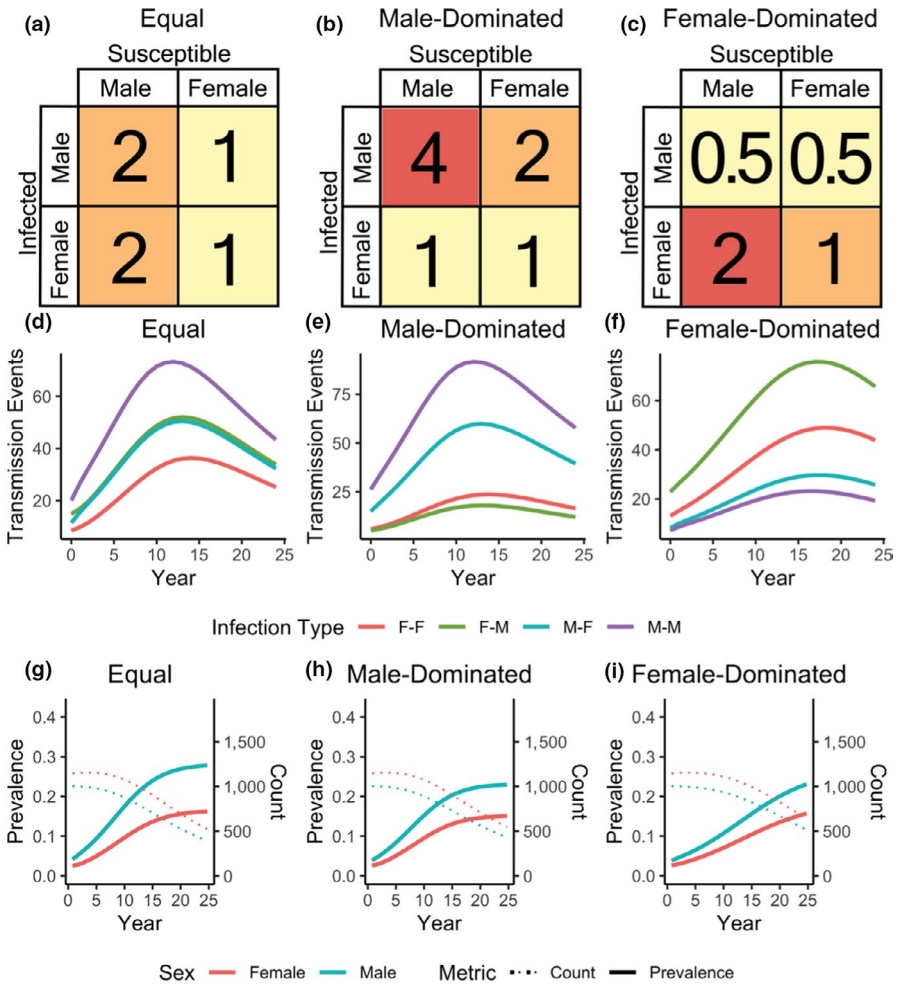

FIGURE 1 (a–c) The weights of γ_{ab} for all sex-to-sex transmission pairings, (d–f) the approximate number of transmission events per month colour-coded by sex-based transmission (F-F for female-to-female, F-M for female-to-male, M-F for male-to-female and M-M for male-to-male), and (g–i) sex-specific chronic wasting disease prevalence (solid lines) and population counts (dashed lines) for equal, male-dominated and female-dominated transmission scenarios. These results assumed mule deer demography and 10% harvests for adult males and females

a mean time to disease-induced mortality of 23 months (5th–95th percentile = 12.62–36.53 months) in the absence of other mortality (based on a gamma distribution with shape = 10, andscale = $\frac{1}{\rho}$), congruent with the experimental trials of CWD infection (Figure S2; Williams, 2005). We did not explicitly model environmentally mediated transmission (see Section 4).

Here, we introduce τ, a distinction from the monthly timestep, t, as we are describing the change in infected individuals after removal by natural mortality, hunting and disease-induced mortality that has already occurred in a month. The number of infections in the first stage of infection ($d = 1$) in an age, c, and sex class, s, at a given timestep is described by Equations 1A and 1B (for female and male infectious classes, respectively):

$$I_{t+1,s=F,c,d=1} = (1-\rho)\, I_{\tau,s=F,c,d=1} + S_{\tau,s=F,c}\left(1 - e^{-\left(\frac{\gamma_{FF}\beta \sum I_{\tau,s=F} + \gamma_{MF}\beta \sum I_{\tau,s=M}}{N_{\tau}^{\theta}}\right)}\right), \quad (1A)$$

$$I_{t+1,s=M,c,d=1} = (1-\rho)\, I_{\tau,s=M,c,d=1} + S_{\tau,s=M,c}\left(1 - e^{-\left(\frac{\gamma_{MM}\beta \sum I_{\tau,s=M} + \gamma_{FM}\beta \sum I_{\tau,s=F}}{N_{\tau}^{\theta}}\right)}\right), \quad (1B)$$

where τ describes a particular month (after mortality), N_{τ} describes the total population in a month and θ describes the scale between frequency- and density-dependent transmission. We considered transmission to be frequency-dependent (Potapov et al., 2013; Samuel & Storm, 2016; Williams et al., 2002) with $\theta = 1$ such that $\gamma_{ab}\beta$ is weighted by the probability of sex-specific encounter and not the abundance of specific sex-to-sex contacts (see Supporting Information for density-dependent simulations).

Harvest mortality ($\kappa_{s,c}$) was assumed to be sex specific and age-specific as well as independent of infection status, assuming hunters cannot discern infection status (Grear et al., 2006; Williams et al., 2002). Finally, harvest mortality was considered to be additive to natural mortality with the rate of survival from November to December defined $\delta_{s,c}(1 - \kappa_{s,c})$.

2.1 | Model assessment and output

At monthly timesteps, the number of individuals in sex-, age- and infection-specific classes were recorded along with cause-specific natural, disease-related or harvest-related mortality. The number of new infections as well as the source of new infectious were also recorded. Following Bjørnstad (2018), we approximated R_0 for this model using the next-generation approach (Equations S1–S3). Approximating R_0 allowed us to compare different parameter sets and transmission coefficients to match our hypothesized transmission scenarios while keeping R_0 roughly equivalent (Table S2). Because males and females are unequal in stable age distributions and demography, R_0 was an important metric to ensure simulated epidemics under different scenarios were largely comparable. However, we note that R_0 alone does not comprehensively describe all epidemic dynamics of interest, and we therefore report sex-specific prevalence and population viability to complement R_0 estimates.

We first investigated the effect of independent male and female harvests (i.e. varying one sex's harvest rate while holding the other sex at a constant rate) on population growth rate (λ at a stable sex and age distribution from the underlying Leslie matrix), R_0 (next-generation approximation from initial conditions), prevalence (infected population divided by the total population at a given time) and population size (susceptible and infected individuals). We then assessed how combinations of adult male and female harvest rates might affect demographic and epidemic outcomes. We created reporting thresholds for CWD prevalence and population size to simplify visualizations of multiple harvest regimes. We established cut-offs of at least 1,000 living individuals (50% of $N_{t=1}$ for all simulations) and <10% CWD prevalence, assessed 5–20 years after simulations onset.

We compared how harvest manipulations can be used to understand transmission mechanisms, by projecting populations under varying rates of adult male and female harvests (low = 5, mid = 10, and high = 15% for female elk; low = 5, mid = 15, and high = 25% for female mule deer; low = 5, mid = 25, and high = 50% for male mule deer and elk) to characterize prevalence over time under the three transmission scenarios. Underlying demographic (according to Raithel et al., 2007) and harvest parameters varied ($\sigma = 0.005$, assumed) with each scenario simulated 50 times.

2.2 | Initial model conditions

We simulated cervid populations with 2,000 individuals ($N = 2{,}000$). Initial model conditions established 4% prevalence for adult females ($N_{s=F,c=3:12}$) and males ($N_{s=M,c=3:12}$), 3% for juveniles ($N_{s=F,c=2}$ and $N_{s=M,c=2}$), and 2% for young of year ($N_{s=F,c=1}$ and $N_{s=M,c=1}$) to remove any potential bias of initial prevalence on later sex-specific prevalence patterns. Starting epidemic conditions had little effect on epidemic outcomes when prevalence for any one category was <10%, besides delaying epidemics with reduced initial prevalence (Figure S20). CWD was introduced to a host population at stable age distribution calculated with the inclusion of adult harvest variation (see Figure S21 for effect of a constant stable sex and age distribution on results) with the POPBIO package (Stubben & Milligan, 2007). We considered harvests between 0% and 50% of adult male for mule deer and elk, 0% and 25% for adult female mule deer and 0% and 14% for adult elk (demographic scenarios that maintained non-zero population sizes over simulation time). We projected populations under varying transmission scenarios and harvest regimes 25 years into the future. All other initial conditions are described in Table S1.

All analyses in this paper were performed in R (version 3.6.3; R Core Team, 2020). The basic transmission model is provided in Cross and Almberg (2019) and code scripts to support the sex- and age-structured model, simulations and analyses are archived with Zenodo (https://doi.org/10.5281/zenodo.5834742).

3 | RESULTS

As expected, the asymptotic population growth rate was most sensitive to changes in adult female survival (Figure S3), while high levels of male harvest were sustainable (Figure 2a). Adult female harvests generally led to population decline (Figure 2a), demonstrating that the model was reflective of empirical data (Gaillard et al., 1998). Harvest scenarios that led to demographic collapse based on initial stable sex and age distributions were not considered.

Increased male harvests reduced prevalence under equal or male-dominated transmission scenarios, yet male harvests were relatively ineffective at controlling the CWD outbreak in female-dominated transmission scenarios (Figure 2b). Prevalence minorly decreased with greater adult female harvests under scenarios that assumed female-dominated transmission (Figure 2b) and demographic costs of female harvests were slightly reduced as compared to other transmission scenarios (Figure 2a), a result of harvests limiting the sex responsible for the majority of CWD transmission (Figure 2a).

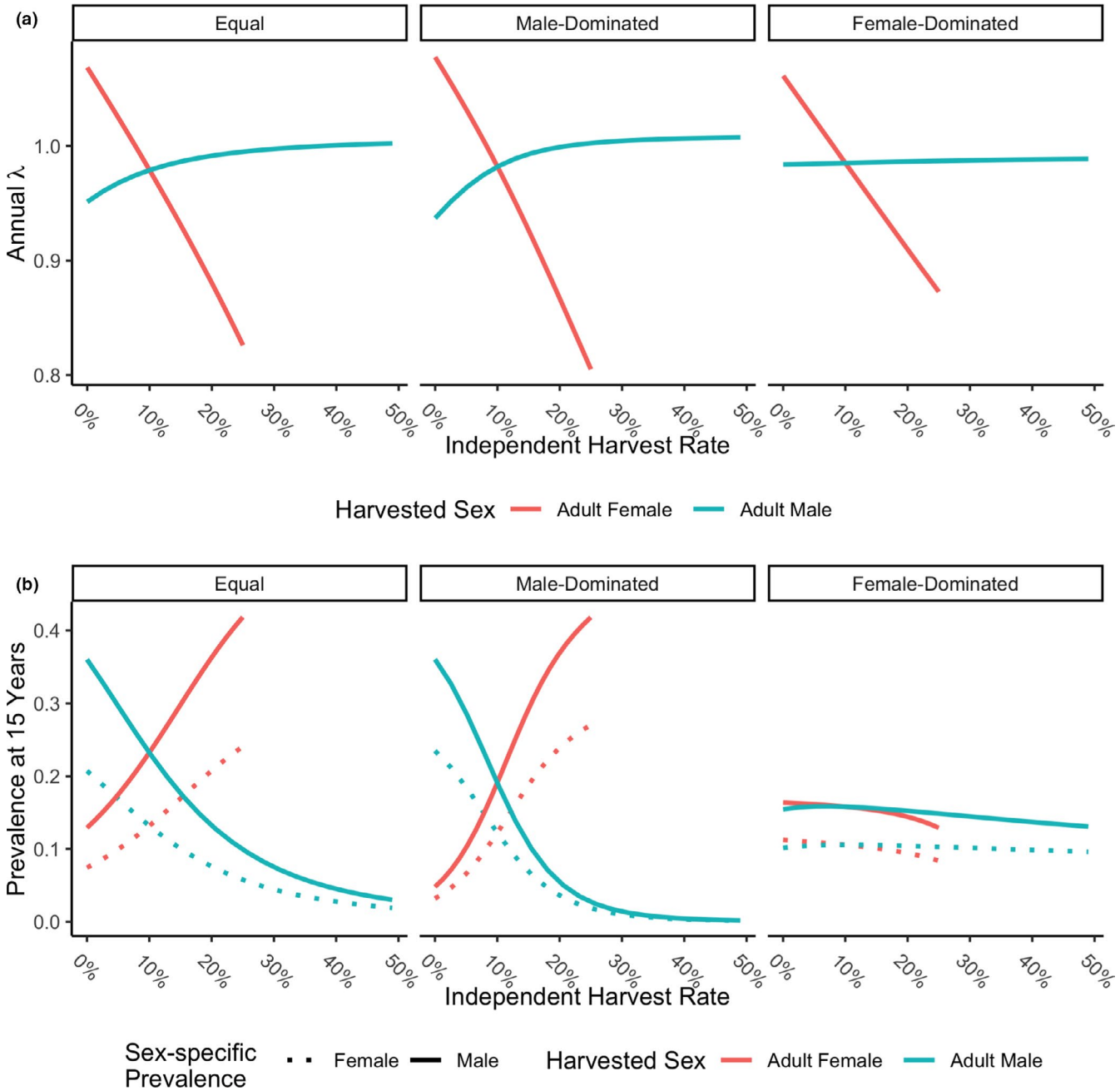

FIGURE 2 (a) Annual change in population, λ, assessed 15 years into simulations and (b) sex-specific chronic wasting disease prevalence assessed 15 years into simulations with independent adult male and female mule deer harvests rates varying from 0% to 50% under equal, female-dominated and male-dominated transmission scenarios. These results assumed mule deer demography and 10% baseline harvests for adults in non-target sexes (i.e. female harvests are 10% for all variable male harvests or blue lines, and male harvests are 10% for all variable female harvests or red lines)

Across all transmission scenarios, increased female harvests led to smaller populations, while male harvests generally caused minor population increases (a result of an initial stable sex and age distribution with more females). Male prevalence was greater than female prevalence across frequency-dependent parameter space; similarly, female population sizes were generally always larger than male population sizes except when female harvests were high (>15%) and male harvests were minimal (<10%; Figures S5 and S16).

For the scenarios we explored, R_0 rarely decreased below one when male and female harvests were considered independently (Figure S4, and only for scenarios with non-zero female harvest), indicating that, conditional on the transmission and demographic parameters chosen, male harvest alone was often insufficient to deter prion invasion. Under equal and male-dominated transmission scenarios, R_0 tended to decrease with greater male harvests (Figure S4). Under female-dominated transmission scenarios, both male and female harvests decreased R_0 to some degree, but too high of female harvests (nearing 20%–25%) caused further increases in R_0 when male harvests were also low (Figure S4)—a result driven by unrealistic sex ratios in initial populations with too high of only female harvest. When male harvests were >20%, female harvests >0% in male-dominated scenarios to >16% in female-dominated scenarios cause R_0 to decrease below one in mule deer simulations (Figure 3 but see for elk Figure S17).

Some results were complex and, at first, appear counterintuitive. When male mule deer harvests were <20%, increasing female mule deer harvests generally caused R_0 to increase under equal and male-dominated scenarios (Figure 3a). Yet, the opposite was true when male harvests were >20% (Figure 3a). This was driven by the female-biased harvests affecting the stable age and sex distribution translating to concentrate highly infectious males. As male harvest rates increase, females (which are less infectious and susceptible than males in these scenarios) are more abundant in the initial stable sex and age distribution and R_0 decreased.

Based on prevalence at 15 years into mule deer simulations, there was no evidence to support increasing female mule deer harvests as a mechanism of decreasing infection prevalence under equal or male-dominated scenarios (Figure 3b; see Figure S5 for sex-specific results). Conversely, it appeared that very high female harvests (>20%) or high male harvests (>30%) were able to reduce prevalence under female-dominated transmission (Figure 3b). As expected, the annual population change estimated at 15 years into simulation time indicated rapid population declines for simulations with high female harvests (Figure 3c). Interestingly, population declines caused by female harvests were dampened under female-dominated transmission than equal or male-dominated scenarios due to decreased transmission and delayed disease-related mortality (Figure 3c).

Demographic and epidemic outcomes were categorically different between equal or male-dominated transmission scenarios and female-dominated transmission (Figure 4)—harvest regimes that were successful under equal or male-dominated transmission failed under female-dominated transmission (also shown for elk; Figures S16–S18). While female-dominated transmission scenarios appeared to have both larger populations and less prevalent disease in year 10, populations declined far more rapidly beyond year 10 than under equal or male-dominated transmission. Equal and male-dominated transmission scenarios had similar demographic and epidemiological outcomes (Figure 4). Under male-dominated or equal scenarios, limited male harvests (<5%–10%) were capable of meeting both the demographic ($N_t \geq 1{,}000$) and epidemic control ($\frac{I_t}{N_t} \leq 0.10$). By year 15 in female-dominated scenarios, no combination of sex-based harvests kept populations high and prevalence low (Figure 4). When adult male harvests were ignored in equal or male-dominated transmission scenarios, populations were demographically viable but incurred high CWD prevalence at least 25 years into simulations (Figure 4).

When considering variation in demographic rates and transmission, many disease transmission scenarios resulted in similar CWD prevalence over the first 10 years when male and female mule deer harvests were low. However, at female harvest levels of 15%–25% female-dominated transmission scenarios more clearly diverge from the other transmission scenarios (Figure 5). Prevalence under female-dominated transmission scenarios was relatively insensitive to changes in male and female harvest rate when opposite sex harvests were fixed at 10% (Figure 5). As a result, female mule deer harvests in the absence of variable male harvests provide little diagnostic utility and are potentially quite risky. Under equal or male-dominated transmission, increasing male harvests caused slight near-term changes in prevalence but male harvests had no real effect under female-dominated transmission (Figure 5). Importantly, prevalence often continues to increase under equal and male-dominated transmission with moderate male harvest rates (25%).

4 | DISCUSSION

Sex- and age-specific disease prevalence is driven by the interaction of exposure and susceptibility, and prevalence alone may not mechanistically describe which groups drive disease transmission. While CWD has been observed at higher prevalence among males than females (DeVivo et al., 2017; Heisey et al., 2010; Miller & Conner, 2005; Miller et al., 2008; Mysterud et al., 2019; Rees et al., 2012; Samuel & Storm, 2016), multiple hypothetical sex-specific transmission scenarios could generate male-biased prevalence (Figure 1). Given that male and female cervid harvests confer contrasting demographic effects, the efficacy of sex-biased harvests on CWD epidemics may be dependent upon transmission dynamics between sexes. In general, female harvests had strongly negative effects on population size and resulted in greater prevalence under male-dominated and equal transmission scenarios. Under frequency-dependent and female-dominated transmission, non-harvest-based mechanisms approaches to disease control may be necessary (density dependence discussed in Supporting Information).

Our model demonstrated that mule deer simulations with large male (>20%) and female harvests (0%–5% under male-dominated transmission to 15%–25% under equal or female-dominated transmission) were capable of producing R_0 values <1 (Figure 3a),

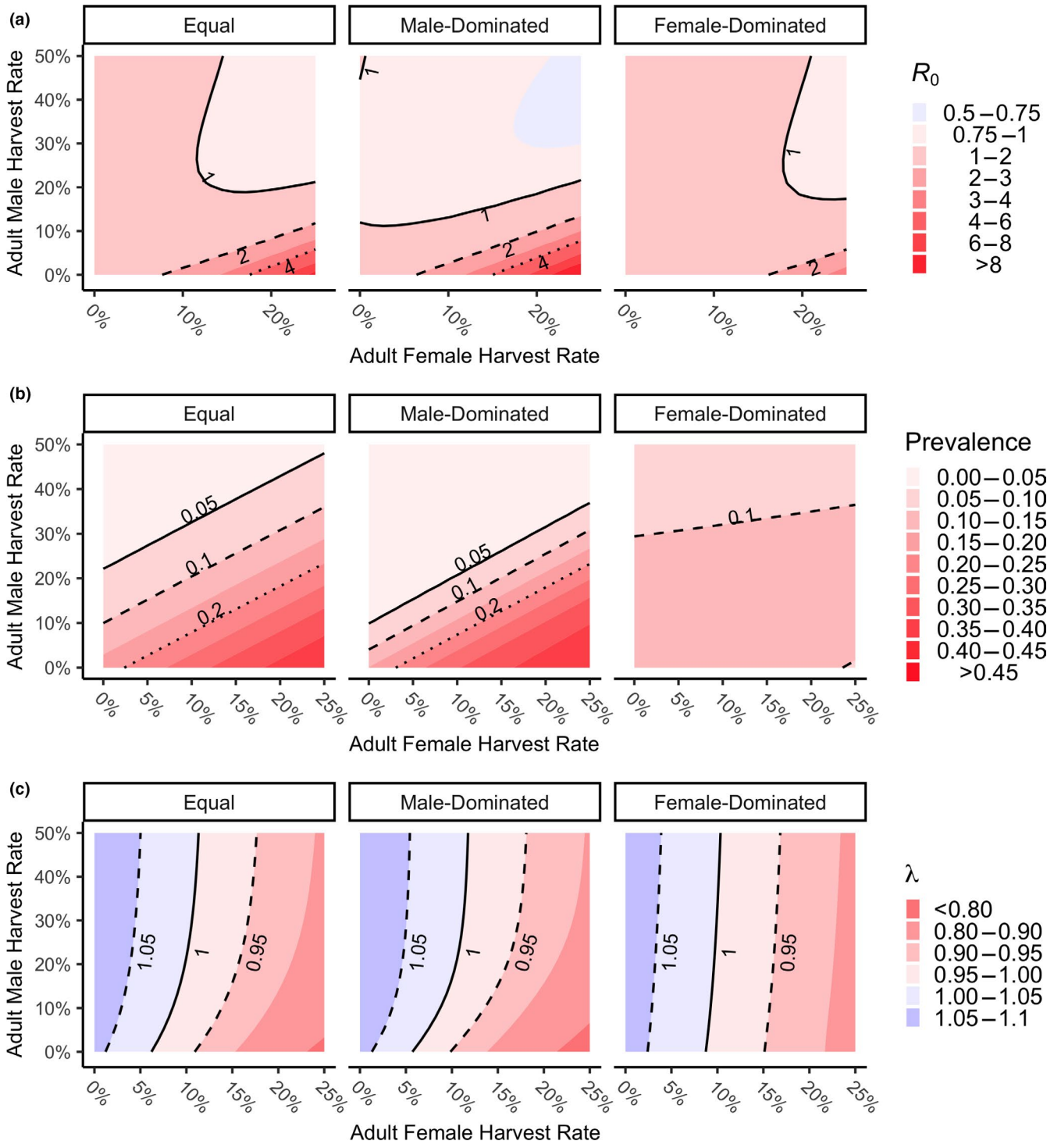

FIGURE 3 (a) R_0, approximated by next-generation matrices, (b) prevalence of chronic wasting disease 15 years into simulations and (c) deterministic population growth rate, λ, based on population size 15 years into simulations across combinations of harvest rates from 0% to 50% for adult males and 0% to 25% for adult females under equal, male-dominated and female-dominated transmission scenarios. Contour lines for R_0 (1.5, 2 and 4), prevalence (0.01, 0.15 and 0.25) and λ (0.95, 1 and 1.05) are also plotted. These results assume mule deer demography

conditional on the transmission and demographic parameters selected. Though populations generally were demographically inviable with high female harvests rates (>20%; Figure 3c). Harvest regimes were successful in limiting prevalence when only male harvests were considered under equal and male-dominated transmission, or heavily weighted either male or female harvests under female-dominated transmission. There was a broad area of the parameter space under equal and male-dominated transmission where population reductions were <50% and CWD prevalence was <10% (typically with <10% adult female harvest and between 0% and 50% adult male

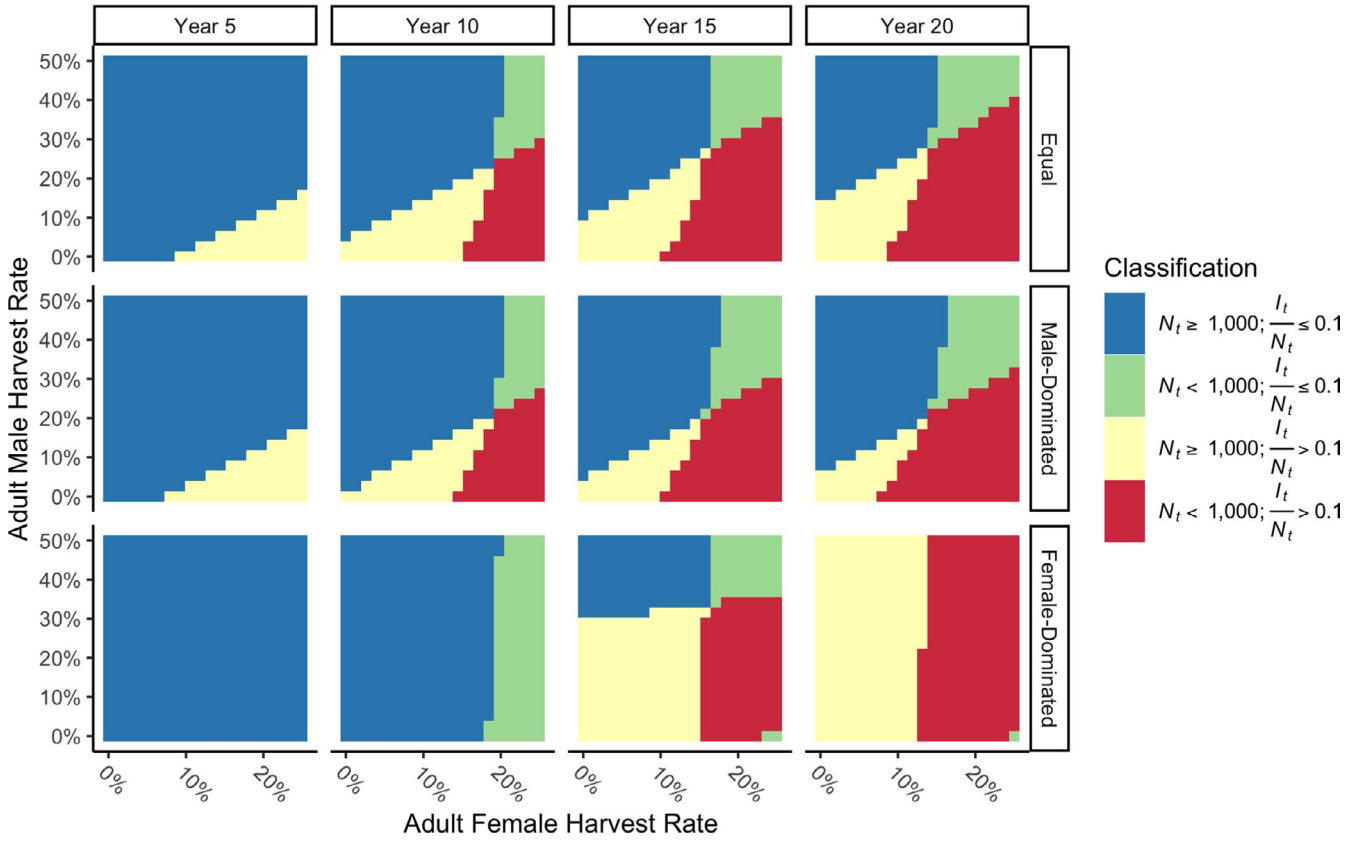

FIGURE 4 The demographic ($N_t \geq 1{,}000$) and epidemic cut-offs ($I_t/N_t \leq 0.10$) based on population size and chronic wasting disease prevalence at 5, 10, 15 and 20 years into simulations with combinations of harvest varying from 0% to 50% for adult males and 0% to 25% for adult females under equal, male-dominated and female-dominated transmission scenarios. The colour of a given cell signifies where a given harvest rate combination met or failed specific criteria under a given transmission scenario. These results assume mule deer demography

harvest). Conversely, female-dominated transmission required female mule deer harvest rates near population failure to regulate prevalence later in epidemics. If transmission is female dominated and males are the recipients, there was no set of hunting parameters explored that resulted in low prevalence and large population sizes beyond 15 years into simulations (Figure 4).

Potapov et al. (2013) demonstrated that sex-biased CWD prevalence is most likely under frequency-dependent transmission, which is supported by field evidence (Jennelle et al., 2014; Storm et al., 2013). Consequently, culls are not likely to alter transmission dynamics between hosts (see Uehlinger et al., 2016). If CWD transmission is density dependent, differences between transmission scenarios may be reduced and harvest-based management may be effective (Figures S8–S12). Furthermore, as environmental transmission may be an important source of prion infections later in an epidemic, intensive harvests and culls may reduce the rate of prion deposition and thus subsequent CWD prevalence (Almberg et al., 2011; Jennelle et al., 2014). Furthermore, harvests are likely incapable of targeting CWD-infected individuals given the difficulty of discerning infection status in preclinical stages (Williams et al., 2002; though infected individuals may be more susceptible). Recognition of male-biased CWD prevalence could inform the implementation of higher male harvests to control CWD. We found that male-biased harvests are likely to be effective when males are more susceptible to CWD than females or males disproportionally transmit CWD to other males.

Females were less likely to be infected than males across all scenarios we considered (Figure S5). As expected, female harvests increased CWD prevalence under equal and male-dominated transmission scenarios. Female harvests increase the abundance of males in the initial stable sex and age distribution, increasing the pool of highly susceptible and contagious host (males) while removing the buffering hosts with lower susceptibility and infectiousness (females). Under female-dominated transmission, female harvests have either a negative or only slightly positive effect on prevalence. While females are less likely to be infected than males, they are not an idle buffer population under female-dominated transmission because they are the most important source of infections in the population (Figure 1f). For example, female harvests had less harmful demographic effects under female-dominated transmission, driven by decreasing disease-related mortality (Figure 3c). This forces a delicate balance in which managers may pursue disease eradication, but concurrently risk the demographic collapse of populations. Less productive populations than considered here may suffer far greater from additional harvest-based female mortality, potentially causing female harvests to be too deleterious to population growth to pursue female harvests for CWD management. We believe that

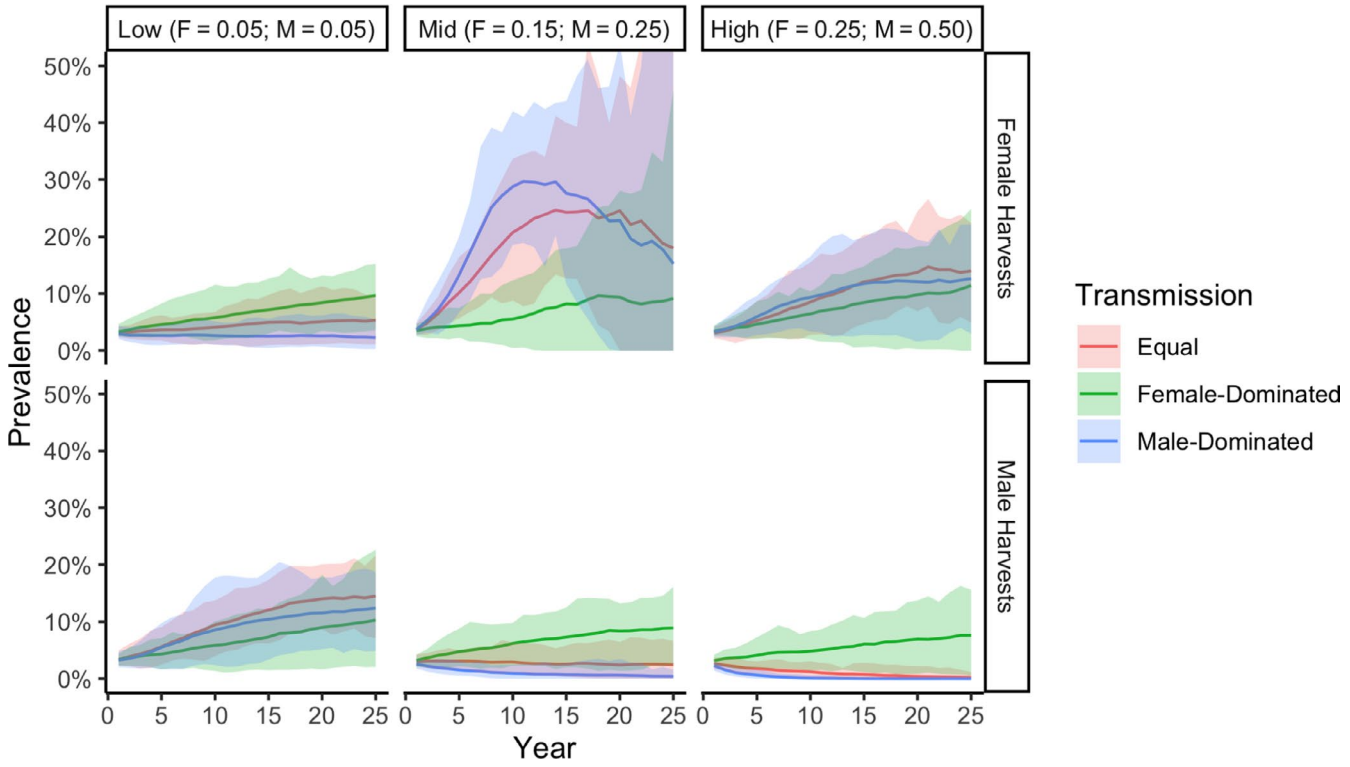

FIGURE 5 Mean prevalence (lines) and 95th percentiles (shaded polygons) over time (0–25 years into simulations) faceted by sex-specific harvest rate and by which sex is targeted by sex-specific harvest rate (5%, 15% and 25% for females while holding male harvests at 10% or 5%, 25% and 50% for males while holding female harvests at 10%) with 50 simulations per scenario. These results assumed mule deer demography with 10% harvests for non-target sexes (i.e. 'female harvests' facets assume 10% male harvest)

understanding how and to what degree sex affects prion transmission is critical to determining how to manage CWD.

Our simulations demonstrate that, by manipulating harvest rates, managers may be able to determine whether prion transmission is dominated by male-controlled mechanisms, like susceptibility and transmission, or by female-to-male transmission. While varying female harvests is a risky mechanism with little diagnostic utility, we showed that herds with varying degrees of male harvest can begin to show differences in prevalence based on transmission scenarios in as few as 5–10 years. A similar strategy focusing only on male harvest rates in reindeer predicted that higher male harvest rates allowed for more rapid removal of CWD from herds (Mysterud et al., 2020), which our results support under scenarios of equal or male-dominated transmission. If females disproportionally contribute to CWD transmission, greater male harvests are ineffective in reducing CWD prevalence even though they hold no real demographic concerns.

Miller et al. (2020) and Conner et al. (2021) both assessed the relationship between increasing male harvests and CWD prevalence, finding that CWD prevalence continued to increase across most regions. These results suggest several non-exclusive possibilities that relate to our modelled results. First, male harvests may not have been aggressive enough to limit prevalence for either the equal or male-dominated scenarios; in our mule deer simulations, male harvest above 25% annually and 50% annually caused declines in prevalence under male-dominated and equal transmission scenarios, respectively (Figure 5). Second, both male and female harvest may be required to lower CWD prevalence under density-dependent transmission, which may be due to direct contact rates (Figure S7) or through an environmental reservoir that increases in importance with an increasing density of infected individuals over time. Finally, increasing CWD prevalence despite high male harvest may be indicative of females playing an important role in disease transmission (Figure 5).

Our demographic model was intended to approximate mule deer and elk populations more broadly (Bender & Hoenes, 2018; Bishop et al., 2005; Forrester & Wittmer, 2013; Gaillard et al., 1998; Lubow & Smith, 2004; Pojar & Bowden, 2004; Raithel et al., 2007; Unsworth et al., 1999; White et al., 1987). We considered adult female and male survival to be largely similar in the absence of harvest (Bishop et al., 2005). As such, our demographic model may represent a highly productive cervid population, leaving more room for error with female harvests. We also considered harvest- and disease-related mortality to be additive to natural mortality. If disease-related mortality were compensatory to natural mortality, the demographic effects detailed here would be dampened. Similarly, our results may be conservative if CWD-infected individuals are more susceptible to harvest (DeVivo et al., 2017). The way in which CWD mortality interacts with natural or harvest-related mortality is currently unclear, yet additive mortality is a plausible assumption based on inferences from population declines associated with CWD outbreaks (DeVivo et al., 2017; Edmunds et al., 2016). CWD mortality may become compensatory as managers adjust harvest rates to account for disease mortality. Additionally, environmental transmission was not

explicitly modelled here, which may increase host prion exposure over time. Limiting population size early in epidemics through female harvests may be important to limit environmental transmission later because environmental transmission is likely related to the density, rather than frequency, of infected individuals over time. Finally, the transition rate between infectious classes was informed by experimental infections which might have more rapid progression of CWD due to the potentially higher challenge doses used in experimental trials. This may make some of our scenarios overly pessimistic, but the general conclusions and relationships we highlight are likely to be robust to this assumption.

Inferences about transmission based on prevalence alone might be misleading (Grear et al., 2012; Perkins et al., 2008). Sex-biased prevalence alone does not inform which sex is responsible for CWD transmission (Potapov et al., 2013) and provides potentially poor criterion for motivating management interventions. Our results suggest that harvest-based assessment of CWD transmission is possible under equal- or male-dominated transmission but potentially requires strong male-based harvests. Miller et al. (2020) and Conner et al. (2021) identified increasing prevalence of CWD under male harvests, potentially indicating more important contributions of females to transmission. However, increases in male prevalence may be possible under too low of male harvest rates even under male-dominated transmission. For female-dominated transmission, it is difficult to maintain large populations with low levels of disease, as high female harvests result in low population sizes but potentially lower prevalence. In this case, managers may need to focus on alternative methods of disease control such as limiting artificial aggregations or novel alternatives to harvest-based management (Joseph et al., 2013).

ACKNOWLEDGEMENTS

Any use of trade, firm or product names is for descriptive purposes only and does not imply endorsement by the U.S. Government. Funding provided by the U.S. Geological Survey.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHORS' CONTRIBUTIONS

W.R., E.E.B. and P.C.C. designed the simulations and wrote the computer code. W.R. wrote and E.E.B. and P.C.C. edited the manuscript. The authorship team and data used in building the model represent geographical regions pertinent to the study.

DATA AVAILABILITY STATEMENT

Model code available via the Zenodo Digital Archive https://doi.org/10.5281/zenodo.5834742 (Rogers et al., 2022) as an addition to Cross and Almberg (2019).

ORCID

Will Rogers https://orcid.org/0000-0001-9899-8064
Ellen E. Brandell https://orcid.org/0000-0002-2698-7013
Paul C. Cross https://orcid.org/0000-0001-8045-5213

REFERENCES

Almberg, E. S., Cross, P. C., Johnson, C. J., Heisey, D. M., & Richards, B. J. (2011). Modeling routes of chronic wasting disease transmission: Environmental prion persistence promotes deer population decline and extinction. *PLoS One*, *6*(5), e19896. https://doi.org/10.1371/journal.pone.0019896

Bender, L. C., & Hoenes, B. D. (2018). Age-related fecundity of free-ranging mule deer *Odocoileus hemionus* Cervidae in south-central, New Mexico, USA. *Mammalia*, *82*(2), 124–132. https://doi.org/10.1515/mammalia-2016-0166

Bishop, C. J., Unsworth, J. W., & Garton, E. O. (2005). Mule deer survival among adjacent populations in Southwest Idaho. *The Journal of Wildlife Management*, *69*(1), 311–321. https://doi.org/10.2193/0022-541X(2005)069<0311:MDSAAP>2.0.CO;2

Bjørnstad, O. N. (2018). *Epidemics: Models and data using R*. Springer.

Chitwood, M. C., Lashley, M. A., Kilgo, J. C., Moorman, C. E., & Deperno, C. S. (2015). White-tailed deer population dynamics and adult female survival in the presence of a novel predator. *The Journal of Wildlife Management*, *79*(2), 211–219. https://doi.org/10.1002/jwmg.835

Clutton-Brock, T. H., Iason, G. R., & Guinness, F. E. (1987). Sexual segregation and density-related changes in habitat use in male and female red deer (*Cerrus elaphus*). *Journal of Zoology*, *211*(2), 275–289. https://doi.org/10.1111/j.1469-7998.1987.tb01534.x

Conner, M. M., Wood, M. E., Hubbs, A., Binfet, J., Holland, A. A., Meduna, L. R., Roug, A., Runge, J. P., Nordeen, T. D., Pybus, M. J., & Miller, M. W. (2021). The relationship between harvest management and chronic wasting disease prevalence trends in western mule deer (*Odocoileus hemionus*) herds. *Journal of Wildlife Diseases*, *57*(4), 831–843. https://doi.org/10.7589/JWD-D-20-00226

Cross, P. C., & Almberg, E. S. (2019). *CWDsims: An R package for simulating chronic wasting disease scenarios (0.1.1)*. U.S. Geological Survey. https://code.usgs.gov/usgs/norock/cross_p/cwdsims

de Vos, A., Brokx, P., & Geist, V. (1967). A review of social behavior of the north American cervids during the reproductive period. *American Midland Naturalist*, 390–417. https://doi.org/10.2307/2423349

DeVivo, M. T., Edmunds, D. R., Kauffman, M. J., Schumaker, B. A., Binfet, J., Kreeger, T. J., Richards, B. J., Schätzl, H. M., & Cornish, T. E. (2017). Endemic chronic wasting disease causes mule deer population decline in Wyoming. *PLoS One*, *12*(10), e0186512. https://doi.org/10.1371/journal.pone.0186512

Edmunds, D. R., Kauffman, M. J., Schumaker, B. A., Lindzey, F. G., Cook, W. E., Kreeger, T. J., Grogan, R. G., & Cornish, T. E. (2016). Chronic wasting disease drives population decline of White-tailed deer. *PLoS One*, *11*(8), e0161127–e0161127. https://doi.org/10.1371/journal.pone.0161127

Foo, Y. Z., Nakagawa, S., Rhodes, G., & Simmons, L. W. (2017). The effects of sex hormones on immune function: A meta-analysis. *Biological Reviews*, *92*(1), 551–571. https://doi.org/10.1111/brv.12243

Forrester, T. D., & Wittmer, H. U. (2013). A review of the population dynamics of mule deer and black-tailed deer *Odocoileus hemionus* in North America. *Mammal Review*, *43*(4), 292–308. https://doi.org/10.1111/mam.12002

Gaillard, J. M., Festa-Bianchet, M., & Yoccoz, N. G. (1998). Population dynamics of large herbivores: Variable recruitment with constant adult survival. *Trends in Ecology and Evolution*, *13*(2), 58–63. https://doi.org/10.1016/S0169-5347(97)01237-8

Grear, D. A., Luong, L. T., & Hudson, P. J. (2012). Sex-biased transmission of a complex life-cycle parasite: Why males matter. *Oikos*, *121*(9), 1446–1453. https://doi.org/10.1111/j.1600-0706.2012.20358.x

Grear, D. A., Samuel, M. D., Langenberg, J. A., & Keane, D. (2006). Demographic patterns and harvest vulnerability of chronic wasting disease infected white-tailed deer in Wisconsin. *The Journal of Wildlife Management*, *70*(2), 546–553. https://doi.org/10.2193/0022-541x(2006)70[546:dpahvo]2.0.co;2

Guerra-Silveira, F., & Abad-Franch, F. (2013). Sex bias in infectious disease epidemiology: Patterns and processes. *PLoS One*, *8*(4), e62390. https://doi.org/10.1371/journal.pone.0062390

Heisey, D. M., Osnas, E. E., Cross, P. C., Joly, D. O., Langenberg, J. A., & Miller, M. W. (2010). Linking process to pattern: Estimating spatiotemporal dynamics of a wildlife epidemic from cross-sectional data. *Ecological Monographs*, *80*(2), 221–240. https://doi.org/10.1890/09-0052.1

Jennelle, C. S., Henaux, V., Wasserberg, G., Thiagarajan, B., Rolley, R. E., & Samuel, M. D. (2014). Transmission of chronic wasting disease in Wisconsin white-tailed deer: Implications for disease spread and management. *PLoS One*, *9*(3), e91043. https://doi.org/10.1371/journal.pone.0091043

Joseph, M. B., Mihaljevic, J. R., Arellano, A. L., Kueneman, J. G., Preston, D. L., Cross, P. C., & Johnson, P. T. J. (2013). Taming wildlife disease: Bridging the gap between science and management. *Journal of Applied Ecology*, *50*(3), 702–712. https://doi.org/10.1111/1365-2664.12084

Lloyd-Smith, J. O., Schreiber, S. J., Kopp, P. E., & Getz, W. M. (2005). Superspreading and the effect of individual variation on disease emergence. *Nature*, *438*(7066), 355–359. https://doi.org/10.1038/nature04153

Lubow, B. C., & Smith, B. L. (2004). Population dynamics of the Jackson elk herd. *The Journal of Wildlife Management*, *68*(4), 810–829. https://doi.org/10.2193/0022-541X(2004)068[0810:PDOTJE]2.0.CO;2

McDonald, J. L., Smith, G. C., McDonald, R. A., Delahay, R. J., & Hodgson, D. (2014). Mortality trajectory analysis reveals the drivers of sex-specific epidemiology in natural wildlife–disease interactions. *Proceedings of the Royal Society B: Biological Sciences*, *281*(1790), 20140526. https://doi.org/10.1098/rspb.2014.0526

Miller, M. W., & Conner, M. M. (2005). Epidemiology of chronic wasting disease in free-ranging mule deer: Spatial, temporal, and demographic influences on observed prevalence patterns. *Journal of Wildlife Diseases*, *41*(2), 275–290. https://doi.org/10.7589/0090-3558-41.2.275

Miller, M. W., Runge, J. P., Holland, A. A., & Eckert, M. D. (2020). Hunting pressure modulates prion infection risk in mule deer herds. *Journal of Wildlife Diseases*, *56*(4), 781–790. https://doi.org/10.7589/jwd-d-20-00054

Miller, M. W., Swanson, H. M., Wolfe, L. L., Quartarone, F. G., Huwer, S. L., Southwick, C. H., & Lukacs, P. M. (2008). Lions and prions and deer demise. *PLoS One*, *3*(12), e4019. https://doi.org/10.1371/journal.pone.0004019

Miller, M. W., Williams, E. S., McCarty, C. W., Spraker, T. R., Kreeger, T. J., Larsen, C. T., & Thorne, E. T. (2000). Epizootiology of chronic wasting disease in free-ranging cervids in Colorado and Wyoming. *Journal of Wildlife Diseases*, *36*(4), 676–690. https://doi.org/10.7589/0090-3558-36.4.676

Mysterud, A., Hopp, P., Alvseike, K. R., Benestad, S. L., Nilsen, E. B., Rolandsen, C. M., Strand, O., Våge, J., & Viljugrein, H. (2020). Hunting strategies to increase detection of chronic wasting disease in cervids. *Nature Communications*, *11*(1), 4392. https://doi.org/10.1038/s41467-020-18229-7

Mysterud, A., Madslien, K., Viljugrein, H., Vikøren, T., Andersen, R., Güere, M. E., Benestad, S. L., Hopp, P., Strand, O., Ytrehus, B., Røed, K. H., Rolandsen, C. M., & Våge, J. (2019). The demographic pattern of infection with chronic wasting disease in reindeer at an early epidemic stage. *Ecosphere*, *10*(11), e02931. https://doi.org/10.1002/ecs2.2931

Mysterud, A., & Rolandsen, C. M. (2018). A reindeer cull to prevent chronic wasting disease in Europe. *Nature Ecology & Evolution*, *2*(9), 1343–1345. https://doi.org/10.1038/s41559-018-0616-1

Perkins, S. E., Ferrari, M. F., & Hudson, P. J. (2008). The effects of social structure and sex-biased transmission on macroparasite infection. *Parasitology*, *135*(13), 1561–1569. https://doi.org/10.1017/S0031182008000449

Pojar, T. M., & Bowden, D. C. (2004). Neonatal mule deer fawn survival in west-Central Colorado. *The Journal of Wildlife Management*, *68*(3), 550–560. https://doi.org/10.2193/0022-541x(2004)068[0550:nmdfsi]2.0.co;2

Potapov, A., Merrill, E., Pybus, M., Coltman, D., & Lewis, M. A. (2013). Chronic wasting disease: Possible transmission mechanisms in deer. *Ecological Modelling*, *250*, 244–257. https://doi.org/10.1016/j.ecolmodel.2012.11.012

Potapov, A., Merrill, E., Pybus, M., & Lewis, M. A. (2016). Chronic wasting disease: Transmission mechanisms and the possibility of harvest management. *PLoS One*, *11*, e0151039. https://doi.org/10.1371/journal.pone.0151039

Raithel, J. D., Kauffman, M. J., & Pletscher, D. H. (2007). Impact of spatial and temporal variation in calf survival on the growth of elk populations. *Journal of Wildlife Management*, *71*(3), 795–803. https://doi.org/10.2193/2005-608

R Core Team. (2020). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing. https://www.R-project.org/

Rees, E. E., Merrill, E. H., Bollinger, T. K., Ten Hwang, Y., Pybus, M. J., & Coltman, D. W. (2012). Targeting the detection of chronic wasting disease using the hunter harvest during early phases of an outbreak in Saskatchewan, Canada. *Preventive Veterinary Medicine*, *104*(1–2), 149–159. https://doi.org/10.1016/j.prevetmed.2011.10.016

Relyea, R. A., Lawrence, R. K., & Demarais, S. (2000). Home range of desert mule deer: Testing the body-size and habitat-productivity hypotheses. *The Journal of Wildlife Management*, *64*(1), 146–153. https://doi.org/10.2307/3802984

Robinson, S. J., Samuel, M. D., O'Rourke, K. I., & Johnson, C. J. (2012). The role of genetics in chronic wasting disease of north American cervids. *Prion*, *6*(2), 153–162. https://doi.org/10.4161/pri.19640

Rogers, W., Brandell, E. E., & Cross, P. C. (2022). *Code to support: Epidemiological differences between sexes affect management efficacy in simulated chronic wasting disease systems*. https://doi.org/10.5281/ZENODO.5834742

Samuel, M. D., & Storm, D. J. (2016). Chronic wasting disease in white-tailed deer: Infection, mortality, and implications for heterogeneous transmission. *Ecology*, *97*(11), 3195–3205. https://doi.org/10.1002/ecy.1538

Storm, D. J., Samuel, M. D., Rolley, R. E., Shelton, P., Keuler, N. S., Richards, B. J., & Van Deelen, T. R. (2013). Deer density and disease prevalence influence transmission of chronic wasting disease in white-tailed deer. *Ecosphere*, *4*(1), art10. https://doi.org/10.1890/ES12-00141.1

Stubben, C., & Milligan, B. (2007). Estimating and analyzing demographic models using the popbio package in R. *Journal of Statistical Software*, *22*(11), 1–23. https://doi.org/10.18637/jss.v022.i11

Tamgüney, G., Miller, M. W., Wolfe, L. L., Sirochman, T. M., Glidden, D. V., Palmer, C., Lemus, A., DeArmond, S. J., & Prusiner, S. B. (2009). Asymptomatic deer excrete infectious prions in faeces. *Nature*, *461*(7263), 529–532. https://doi.org/10.1038/nature09031

Uehlinger, F. D., Johnston, A. C., Bollinger, T. K., & Waldner, C. L. (2016). Systematic review of management strategies to control chronic wasting disease in wild deer populations in North America. *BMC Veterinary Research*, *12*(1), 173. https://doi.org/10.1186/s12917-016-0804-7

Unsworth, J. W., Pac, D. F., White, G. C., & Bartmann, R. M. (1999). Mule deer survival in Colorado, Idaho, and Montana. *The Journal of Wildlife Management*, 315–326. https://doi.org/10.2307/3802515

VanderWaal, K. L., & Ezenwa, V. O. (2016). Heterogeneity in pathogen transmission: Mechanisms and methodology. *Functional Ecology*, *30*(10), 1606–1622. https://doi.org/10.1111/1365-2435.12645

Wearing, H. J., Rohani, P., & Keeling, M. J. (2005). Appropriate models for the management of infectious diseases. *PLoS Medicine*, *2*(7), e174. https://doi.org/10.1371/journal.pmed.0020174

White, G. C., Garrott, R. A., Bartmann, R. M., Carpenter, L. H., & Alldredge, A. W. (1987). Survival of mule deer in Northwest Colorado. *The Journal of Wildlife Management*, 852–859. https://doi.org/10.2307/3801751

Williams, E. S. (2005). Chronic wasting disease. *Veterinary Pathology*, *42*(5), 530–549. https://doi.org/10.1354/vp.42-5-530

Williams, E. S., Miller, M. W., Kreeger, T. J., Kahn, R. H., & Thorne, E. T. (2002). Chronic wasting disease of deer and elk: A review with recommendations for management. *The Journal of Wildlife Management*, 551–563. https://doi.org/10.2307/3803123

Williams, E. S., & Young, S. (1980). Chronic wasting disease of captive mule deer: A spongiform encephalopathy. *Journal of Wildlife Diseases*, *16*(1), 89–98. https://doi.org/10.7589/0090-3558-16.1.89

Wolfe, L. L., Miller, M. W., & Williams, E. S. (2004). Feasibility of "test-and-cull" for managing chronic wasting disease in urban mule deer. *Wildlife Society Bulletin*, *32*(2), 500–505. https://doi.org/10.2193/0091-7648(2004)32[500:fotfmc]2.0.co;2

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Rogers, W., Brandell, E. E. & Cross, P. C. (2022). Epidemiological differences between sexes affect management efficacy in simulated chronic wasting disease systems. *Journal of Applied Ecology*, 59, 1122–1133. https://doi.org/10.1111/1365-2664.14125